High-Dose Olanzapine Orally Disintegrating Tablets for Treatment-Resistant Psychosis

Sir: Olanzapine is a thienobenzodiazepine antipsychotic that has a broad in vitro affinity for several receptors, including serotonergic, cholinergic, dopaminergic, and adrenergic receptors.[1] Olanzapine is approved for treatment of psychoses at doses up to 20 mg/day.[2] New research suggests benefits of higher doses of olanzapine.[3] Anecdotal case reports highlight the benefits of olanzapine at 50 mg/day in patients with refractory schizoaffective disorders.[4] In the United Kingdom, a trial of high-dose olanzapine (range, 20–60 mg/day) showed moderate to marked clinical improvement in patients with clozapine-resistant schizophrenia.[5]

Treatment-resistant psychosis is generally treated with clozapine, which requires frequent blood tests and is associated with several side effects, including weight gain, sedation, and agranulocytosis. Regular blood draws and the myriad of side effects often contribute to poor compliance with clozapine. However, when patients fail clozapine, few other options exist. We describe a patient who, after failing clozapine treatment, responded to the orally disintegrating formulation of high-dose olanzapine.

Case report. Mr. A, a 44-year-old man, had a long history of schizoaffective disorder, bipolar type (DSM-IV criteria). Symptoms started at the age of 21 years and included auditory hallucinations, delusions of grandeur, and hyper-religiosity. He was hospitalized multiple times and, at the time of the presentation described here (1999), was being treated in an assertive community training (ACT) program.

After several medication failures, including trials of risperidone, quetiapine, ziprasidone, and olanzapine, he started clozapine treatment. All previous antipsychotic medications were administered for an adequate duration at an adequate dose; the maximum dose of olanzapine prescribed in the past was 20 mg/day. He developed disabling fatigue soon after initiation of treatment with clozapine. He often missed his appointments because of his dislike of frequent blood tests; however, after staff members from ACT began working closely with Mr. A, his compliance improved, as demonstrated by therapeutic serum clozapine levels, but his psychosis continued. He subsequently stopped clozapine and had a relapse of symptoms, including an increase in hallucinations and delusions that required hospitalization.

During hospitalization, Mr. A was administered the orally disintegrating formulation of olanzapine; this formulation improved his medication adherence, but his psychotic symptoms continued. After 2 weeks of treatment with olanzapine, the dose was increased to 40 mg daily. He reported a decrease in auditory hallucinations and hyper-religiosity and continued to deny side effects. His family reported improvement in his social functioning and cognition. On the basis of his symptoms, olanzapine was titrated further to 60 mg daily. His condition improved, and he experienced no side effects.

Over the next 3 months, his psychosis continued to decrease. His Brief Psychiatric Rating Scale[6] score decreased from l4 (with clozapine) to 3 (with orally disintegrating olanzapine) on objective evaluation and from 6 to 2 on subjective evaluation. Disorganized thoughts and somatic preoccupations decreased significantly. His serum olanzapine level was 108.3 ng/mL (therapeutic range: 20–60 ng/mL).

Mr. A had gained weight from 210 lb to 276 lb while taking a combination of valproic acid and clozapine prior to initiation of olanzapine. Weight gain and glucose dysregulation are known side effects associated with use of olanzapine.[7–9] Several measures, including periodic monitoring of weight, diet management, and encouragement for regular exercise, were provided as part of the ACT program to counter the above-mentioned side effects. Mr. A was compliant with the recommendations and lost 10 lb over a period of 2 years. Periodic glucose monitoring showed no glucose dysregulation. Over the next year, he required no hospitalization, his level of independent functioning improved, and he resumed his education at a community college.

The patient's improvement was probably multifactorial, but higher doses of olanzapine and the orally disintegrating formulation might have played a part. Use of olanzapine was not accompanied by the fatigue associated with clozapine and improved medication adherence. Prescribing guidelines for olanzapine suggest a maximum dose of 20 mg/day. Higher-dose olanzapine treatment has not been well researched, but in our patient, it was efficacious and produced fewer side effects than clozapine. Further, obviating the need for blood draws and use of orally disintegrating pills improved medication adherence and reduced the need for monitoring. Most importantly, the patient's symptoms improved without additional side effects. Since he had previously not responded to low-dose olanzapine, clinical improvement after starting higher doses of olanzapine suggests causality.

Although more clinical trials are needed to establish the benefits of high-dose olanzapine treatment, it may be an option for patients with treatment-resistant psychosis. High-dose olanzapine in the orally disintegrating formulation offers several advantages, including ease of administration, limited need for blood draws, and potential for improved mood stabilization.

The authors report no financial affiliation relevant to the subject of this letter.

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Aerophagia as the Initial Presenting Symptom of a Depressed Patient

Sir: As reported in the recently published article by Haug et al.,[1] gastrointestinal symptoms are reported in as much as 50% of the general population and are even more common in patients with a diagnosis of an anxiety or depressive disorder. One particular gastrointestinal complaint is aerophagia, which is "a repetitive pattern of swallowing or ingesting air and belching."[2] Air swallowing, whether inadvertent or purposeful, is not an uncommon symptom of psychopathology.[3] The following case report describes a patient with depression and concomitant aerophagia. Interestingly, the patient initially presented to a health care professional with a chief complaint of chronic and intractable belching and was later diagnosed with depression. This case serves to reinforce the importance of a psychiatric assessment within the primary care setting.

Case report. Ms. A, a 78-year-old married white woman with no prior psychiatric history, initially presented to a psychiatrist following 1 year's duration of chronic belching. There was no reported family history of psychiatric illness. She reported that her own birth occurred after normal gestation and delivery and reached appropriate developmental milestones without any childhood illnesses. She attended 1 year of business college without obtaining a degree and worked as a bank teller until she married her present husband of 54 years. They have 1 son, who lives nearby.

Her medical history is significant for Graves disease, which was treated medically 20 years ago. She also had an episode of temporal arteritis in 1986 that was successfully treated with prednisone at that time. Additionally, she is known to have mitral valve prolapse, osteoporosis, and gastroesophageal reflux disease.

She began experiencing chronic belching in the spring of 2003, which prompted a complete gastrointestinal workup including an upper gastrointestinal and small bowel series, upper and lower endoscopies, gastric emptying study, and abdominal computed tomography. She reported that her belching was continuous except while asleep, and it seemed to be exacerbated by stress. Nausea accompanied her belching, but she denied any vomiting. All studies failed to show a medical reason for her chronic belching, and she was diagnosed with aerophagia secondary to her anxiety and promptly referred to a psychiatrist.

Upon the initial psychiatric assessment, Ms. A also described concomitant psychiatric symptoms that occurred within the same time frame as her chronic belching. She and her husband described her as having a depressed mood for the last year as well as having the inability to laugh or cry. Her sleep had been poor with frequent early morning awakenings. Ms. A also complained of fatigue, poor concentration, and anhedonia. Over the last 2 years, she had noticed a decrease in her appetite and estimated that she had lost approximately 25 pounds. She denied ever having suicidal ideation or a passive death wish. Additionally, her husband noted that she was much more anxious than she had been premorbidly.

After her initial psychiatric visit, the patient was placed on treatment with escitalopram and trazodone, without success. She was then admitted to a psychiatric facility for medication management with inpatient monitoring. During her admission, a video esophagogram found that the patient had a cascading stomach that could have contributed to her chronic belching. Her prior antidepressant was discontinued, and she was subsequently treated with nortriptyline up to a dose of 35 mg and was also placed on an empirical trial of chlorpromazine 10 mg. She was discharged from the hospital and has since had several months free from chronic belching and depressive symptomatology.

To make a diagnosis of aerophagia, 2 criteria must be met: (1) the patient must be observed swallowing air and (2) the patient must experience repetitive belching.[2] The above conditions must occur at least 12 weeks out of a year and must be troublesome. Patients with aerophagia typically swallow air unconsciously, and it is thought that it is a learned habit. The vast majority of patients with aerophagia actually have an increased frequency of normal swallowing, whereas swallowing large volumes of air is more characteristic of institutionalized patients with aerophagia.[4] Increased swallow frequency is postulated to be secondary to stress or anxiety. Therefore, patients with aerophagia should be screened for psychiatric illnesses as this can be a common symptom of depression and anxiety.[3]

If aerophagia is a consequence of a psychiatric illness, then the underlying disease should be treated. Additionally, a study by Calloway et al.[5] has suggested that biofeedback may be useful. Although dietary modifications are usually suggested (i.e., eating slowly, taking small swallows, and avoiding carbonated drinks), they are rarely successful.[2] Because stress is thought to contribute to aerophagia, stress reduction techniques could also prove useful.

After a psychiatric diagnostic interview, our patient was found to be suffering from a major depressive episode and had considerable anxiety. She was treated with nortriptyline for her depression and chlorpromazine as an empirical treatment for her aerophagia. Although chlorpromazine is known to be useful in the treatment of intractable hiccups, it is unlikely that the resolution of the patient's symptoms was secondary to chlorpromazine's putative mechanism of action, which is to disrupt the hiccup reflex arc.[6] Instead, the chlorpromazine most likely aided her via its anxiolytic properties.

In summary, gastrointestinal complaints are commonplace both in the general population and especially in the psychiatric population. Patients who present with aerophagia should be adequately screened for psychiatric illnesses. If aerophagia is diagnosed, there are several behavioral modifications that can be recommended in addition to treating the underlying disorder.

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